<Division of Biochemistry> Chemical Biology

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- Chemical Biology -

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Visitors

Prof SAZER, Shelley	Baylor College of Medicine, USA, 28 September 2005
Prof HAN, Kyou Hoon	Korea Research Institute of Bioscience and Biotechnology, Korea, 8 November 2005
Prof SUZUKI, Hisanori	University of Verona, Italy, 30 November 2005

Scope of Research

In human history, small organic molecules have been utilized for improving human health and for revealing secrets of life. Discovery or design of small organic molecules with unique biological activity permits small-molecule-initiated exploration of biology and further understanding of human diseases. Our laboratory has been discovering small organic molecules that modulate transcription or differentiation to use them as tools to explore biology. Such chemistry-initiated biology is recently called chemical biology, an emerging field of biology and medical sciences. Although our chemical biology is a basic one, it may "catalyze" future drug discovery.

Research Activities (Year 2005)

Presentations

Chemical Biology of Gene Expression and Cell Differentiation, Uesugi M, 78th National Meeting of Japanese Society of Pharmacology, Yokohama, Japan, 22 - 24 March 2005.

Modulation of Gene Expression by Targeting a Protein-protein Interaction, Uesugi M, 12th International Molecular Medicine Tri-Conference, San Francisco, USA, 19 - 22 April 2005.

Synthetic Small Molecules that Modulate Gene Expression and Cell Differentiation, Uesugi M, 20th International Combinatorial Chemistry Symposium, Osaka, Japan, 25 - 26 April 2005.

Poly(ADP-ribose)polymerase-1 Activation and Mitochondrial Impairment *in vitro* Model of Cerebral Ischemia, Tanaka S, 20th Biennial Meeting of the ISN Satellite Symposium "Molecular Basis for Signal Transduction in Neurodegeneration and Neuroregeneration", Warsaw, Poland, 26 August - 1 September 2005.

Poly(ADP-ribose)polymerase-1 Activation and Mitochondrial Impairment in *in vitro* Model of Cerebral ischemia, Tanaka S, 18th National Convention on ADP-ribosylation Process, Verona, Italy, 3 - 4 October 2005.

Regulation of NF-κB and AP-1 by PARP-1 in Reactive Astrocytes of Alzheimer's Disease, Tanaka S, 14th International Meeting of ADP Ribosylation Reactions, "PARP2005: Bench to Bedside", Newcastle, UK, 5 - 7 October 2005.

Chemical Biology of Gene Expression and Cell Differentiation, Uesugi M, 6th Australian Peptide Conference, Hamilton Island, Queensland, Australia, 9 - 14 October 2005.

Chemical Biology of Gene Expression and Cell Differentiation, Uesugi M, Pacifichem 2005 Symposium, "Chemical Biology: Small Chemical Compounds As Magic Bullets To Elucidate Biological Mechanisms", Honolulu, Hawaii, 15 - 20 December 2005.

Grants

Uesugi M, Small Molecule Transcription Factors that

Small-Molecule-initiated Biology

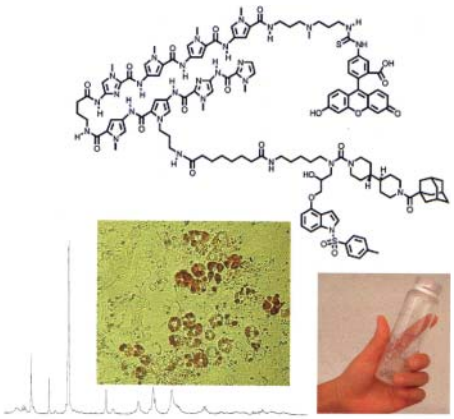
Our current research programs focus on discovering and designing small organic molecules that modulate gene transcription or cell differentiation and using them as tools to explore biology. Regulation of gene transcription and cell differentiation often induces drastic phenotypic changes in living organisms. Precise, external control over these endogenous processes through small organic molecules represents a challenge of chemistry to nature. The latest achievements are summarized below.

Discovery of organic compounds that modulate transcription. Our group isolated human Sur-2, a Ras-linked subunit of the human mediator complex, as a nuclear factor that plays a critical role in overexpression of Her2 in breast cancer cells. This achievement was well appreciated in the oncology field because Her2 is a clinically important oncogene whose overexpression occurs in ~30% of breast cancer patients. Our group showed, by a combination of biochemical and NMR experiments, that Sur-2 protein interacts with a short alpha-helical motif in the activation domain of ESX transcription factor to activate Her2 transcription.

We also discovered a small-molecule inhibitor of the ESX-Sur2 interaction by a screening of a focused chemical library. The compound that we named "adamanolol" represents the first small molecules that modulate gene transcription by targeting transcription factor-coactivator interaction. Our group, as a collaboration with another laboratory, synthesized adamanolol and its derivatives and obtained structure-activity relationship, which enabled the design of the second-generation compound named "wrenchnolol." The wrench-shaped compound is now recognized in the field as a highly unique synthetic molecule that controls gene expression.

Wrenchnolol mimics an alpha-helical activation domain of ESX: it may serves as a small-molecule activation module when coupled with a DNA binding molecule. Our group, as a collaboration with Dervan's group, has recently succeeded in designing a completely organic, synthetic transcription factor that activates transcription. This work demonstrates that it is possible to generate a transcription factor out of organic compounds.

Discovery of organic molecules that modulate cell differentiation. Our group has developed a unique method of screening chemical libararies for the discovery of bioactive molecules. In our approach, chemical compounds were first profiled by their effects on phenotypic fat cell differentiation and pre-selected for more focused secondary assays. This approach enebled us to discover a number of bioactive compounds with interesting biological activities, and these molecules are now used for elucidation of new biological pathways in our group. For example, we recently discovered a new signaling pathway to control insulin/IGF pathways by utilizing the compound we call chromeceptin.



Roles of Poly(ADP-ribose) polymerase-1 in Alzheimer's Disease

Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear enzyme that catalyzes formation of $(ADP\text{-}ribose)_n$ chains on acceptor proteins including histones and PARP-1 itself. PARP-1 is termed a "guardian of the genome", because it assists DNA repair by sensing DNA damage. In the present year, our group investigated a role of PARP-1 in transcriptional regulation and Alzheimer's disease (AD) pathogenesis. Our group examined the effects of PARP-1 siRNA on the DNA-binding activities of a range of transcription factors. Among transcription factors examined, NF-κB and AP-1 were found to increase their DNA binding activity in astrocytes after the addition of β-amyloid, whereas the increase of their DNA-binding was suppressed by PARP-1 siRNA in a dose-dependent manner. NF-κB and AP-1 are the transcription factors involved primarily in expression of proinflammatory or cytotoxic factors in AD astrocytes, and PARP-1 plays a critical role as a coactivator in their transcriptional activation. It is an exciting prospect that manipulation of the PARP-1 expression may serve as a novel therapeutic intervention in the treatment of AD.

can be Used for Biological Investigation, Precursory Research for Embryonic Science and Technology, Japan Science and Technology Agency, 1 October 2005 - 31 March 2009.

Tanaka S, Study on the Function of NAD^+ and ADP-ribose as Stress Mediator, Japan Foundation for Applied Enzymology, 1 April 2005 - 31 March 2006.